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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/926,391	01/08/2002	Eiji Shiojiri	215409US0	9970

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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 08/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/926,391	SHIOJIRI ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-19 and 24-41* is/are rejected.

7)☒ Claim(s) *3 and 20-23* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/21/06 & 7/6/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Request for Continued Examination (RCE) filed June 21, 2006 under 37 CFR 1.114 is acknowledged. An action on the RCE follows.

Status of the Claims

2. Claims 1 and 3-41 are pending.

Applicants' amendment and Declaration of Eiji Shiojiri and Yoshinobu Takino filed June 21, 2006 are acknowledged. Applicant's response and Declaration of Eiji Shiojiri and Yoshinobu Takino have been fully considered. Claims 1, 3-5, 8-27 and 30-41 have been amended. Therefore, claims 1 and 3-41 are examined.

Priority

3. Applicant claims foreign priority under 35 USC § 119(a)-(d), however, applicant has not provided an English translation of the priority document (Japan Application No. 11/118633). Therefore, the priority date (4/26/1999) is not perfected. The priority date of the instant application is the filing date of PCT/JP00/02687, April 25, 2000.

Withdrawn Claim Rejections - 35 USC § 112

4. The previous rejection of claim 25, under 35 U.S.C. 112, second paragraph, is withdrawn in view of applicants' amendment to the claim, and applicants' response at page 23 in the amendment filed June 21, 2006.

Withdrawn Claim Rejections - 35 USC § 103

5. The previous rejection of claim 1 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Iwama et al. (U.S. Patent 3,619,196), is

withdrawn in view of applicants' amendment to the claim, and applicants' response at pages 22-23 in the amendment filed June 21, 2006.

6. The previous rejection of claim 24 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Isler (U.S. Patent 2,179,979), is withdrawn in view of applicants' amendment to the claim, and applicants' response at pages 22-23 in the amendment filed June 21, 2006.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 4-19 and 24-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Response to applicant's argument is shown below.

Claims 1, 4-19 and 24-41 are directed to a compound having a naphthyl group and represented by Formula (1), which includes a dipeptide (when n=0, m=1 in claim 1, or n=1, m=0 in claim 24), and a tripeptide (when n=1, m=1 in claim 24); a melanocyte-stimulating hormone (MSH) inhibitory composition, a whitening agent or a cosmetic or external preparation for the skin comprising the compound of Formula (1) as the active ingredient; and a method of whitening, regulating immunofunction or regulating appetite in a subject using the compound of Formula (1). While the specification indicates that the invention provides di- or tri-peptide

derivatives with the Formula (1) having a naphthyl group, which can inhibit the action of melanocyte-stimulating hormone, thereby the compound can be used as an active ingredient in a melanocyte-stimulating hormone inhibitory composition, a whitening agent, an immunofunction controlling agent, an appetite controlling agent, or a cosmetic preparation (pages 3-6), the specification does not disclose a genus of variants for the active compounds of Formula (1) having inhibitory activity against MSH and their use as an active ingredient in a MSH inhibitory composition, a whitening agent or a cosmetic preparation, or in the method of whitening, regulating immunofunction or regulating appetite in a subject.

The specification merely discloses specific compounds of Formula (1) such as D-1-Nal-Arg-LeuNH$_2$, D-2-Nal-Arg-LeuNH$_2$, L-1-Nal-Arg-LeuNH$_2$, and L-2-Nal-Arg-LeuNH$_2$ have inhibitory activity against MSH (test Example 1), suppress the melanin formation (text Example 2), and suppress pigmentation in brown guinea pig model (test Example 4), it does not identify any active naphthoyl dipeptide compounds (compounds in claim 1) or naphthyl dipeptide compounds (compounds in claim 24) among numerous compounds of Formula (1) (e.g., compounds with undefined substituents in R^1, R^2 and R^3 being a substituted straight-chain or branched-chain C_{1-6} alkyl group having one or more substituents; compounds with undefined substituents in R^4 being a substituted basic amino acid having one or more substituents), nor discloses any particular structure to function/activity relationship in the compounds of formula (1), especially those having various substituents. Furthermore, the specification does not disclose a genus of variants for "functional" compounds of formula (1) including dipeptides and tripeptides as active ingredients in the method of whitening, regulating immunofunction or regulating appetite in a subject. The skilled artisan cannot envision all the contemplated

compounds of formula (1) having inhibitory activity against MSH, or as a whitening agent, an immunofunction controlling agent, or an appetite controlling agent based upon four specific naphthyl-tripeptides having Nal-Arg-Leu sequence. Without guidance on the correlation of structure to function/activity for the compounds of formula (1), one skilled in the art would not know which groups on dipeptides or tripeptides of compounds of formula (1) are essential for function/activity, and which compound of formula (1) is functional. The lack of a structure to function/activity relationship in the compounds of formula (1), and the lack of representative species as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise terms that a skilled artisan would not recognize applicants were in possession of the claimed invention.

Response to Arguments

Applicants indicate the specification has detailed description at pages 5 and 8-16 of the genus of variants for the compounds of Formula (1), and provides a full and detailed description of how to identify an active amino acid, dipeptide or tripeptide compound within the scope of formula (1) at page 16, line 12 to page 19, line 2; further, pages 19-24 describe how the skilled artisan would prepare compositions containing the compounds meeting the claimed activity limitation; and the specification has exemplified several synthetic methods to produce compounds of Formula (1) and methods by which the activity of the same may be ascertained at pages 25-43; and Test Examples 1, 2, and 4 by which the skilled artisan may readily identify functional compounds. Furthermore, a Declaration of Drs. Eiji Shiojiri and Yoshinobu Takino presents a diverse spectrum of compounds within the scope of the claimed invention were

prepared and were assayed for melanocyte-stimulating hormone (MSH) inhibitory activity, thus the skilled artisan can readily produce the compounds of the claimed invention and can readily identify the active compounds, especially those that have inhibitory activity against MSH. In view of the foregoing, applicants request withdrawal of this ground of rejection (pages 19-21 of the response).

Applicant's response and the Declaration of Drs. Eiji Shiojiri and Yoshinobu Takino have been considered, however, the arguments are not found persuasive because of the following reasons. The specification merely describes numerous variants for compounds of formula (1) (e.g., compounds with undefined substituents in R^1, R^2, R^3 and/or R^4) and identifies four specific Nal-Arg-Leu tripeptides having inhibitory activity against MSH, it has not described a genus of variants for functional compounds of formula (1), nor has established the correlation of structure to function/activity for the compounds of formula (1), especially those having various substituents in R^1, R^2, R^3 and/or R^4. For example, compounds of Formula (1) of claims 1 and 24 without recitation of the function would contain numerous dipeptides and tripeptides, and no active naphthyl-containing dipeptides have been identified. Although methods to identify an active compound as inhibitor against MSH and synthetic methods to make compounds of formula (1) have been disclosed, the specification has not established the correlation of structure to function/activity for the compounds of formula (1), especially those having various substituents, thus one skilled in the art could not readily identify a dipeptide or tripeptide among numerous compounds of formula (1) without testing all the candidate compounds.

In the Declaration of Drs. Eiji Shiojiri and Yoshinobu Takino, additional 16 compounds have been presented. However, compounds **8-16** are not within the scope of the claimed

invention since they do not contain "naphthyl" group, only compounds **1-7** are within the scope of compounds of Formula (1). Among these 7 compounds, only compound 6 is Nal-Arg dipeptide, the rest are Nal-Arg-Leu tripeptides with three different acyl group in Y, Nal-Lys-Leu, and Nal-Lys-Trp tripeptides, there are no representative compounds for compounds of formula (1) having various substituents that are active in inhibition against MSH, or as a whitening agent, an immunofunction controlling agent, or an appetite controlling agent.

Since applicants have failed to sufficiently describe the claimed invention, a skilled artisan would not recognize applicants were in possession of the claimed invention. Therefore, the rejection is maintained.

8. Claims 8-10, 12-14, 16-18, 30-32, 34-36 and 38-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of suppressing pigmentation of skin in a mammal by topically administering to the mammal the compound of D-1-Nal-Arg-LeuNH$_2$, D-2-Nal-Arg-LeuNH$_2$, L-1-Nal-Arg-LeuNH$_2$, and L-2-Nal-Arg-LeuNH$_2$, does not reasonably provide enablement for a method of whitening, regulating immunofunction or regulating appetite in a subject by administering an agent comprising the compound of Formula (1). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 8-10, 12-14, 16-18, 30-32, 34-36 and 38-40 encompass a method of whitening, regulating immunofunction or regulating appetite in a subject by administering an agent comprising the compound of Formula (1); and a whitening agent comprising the compound of Formula (1). The specification, however, only discloses cursory conclusions without data

supporting the findings, which state that the present invention provides di- or tri-peptide derivatives with the Formula (1) having a naphthyl group, which can inhibit the action of melanocyte-stimulating hormone, thereby the compound can be used as an active ingredient in a melanocyte-stimulating hormone inhibitory composition, a whitening agent, an immunofunction controlling agent, an appetite controlling agent, or a cosmetic preparation (pages 3-6). There are no indicia that the present application enables the full scope in view of a method of whitening, regulating immunofunction or regulating appetite in a subject by administering an agent comprising the compound of Formula (1) as discussed in the stated rejection. The present application does not provide sufficient teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the absence or presence of working examples, the state of the prior art and relative skill of those in the art, the predictability or unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding various compounds of Formula (I) and their effects in whitening, regulating immunofunction or regulating appetite in a subject, which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

The specification merely discloses specific compounds of Formula (1) such as D-1-Nal-Arg-LeuNH$_2$, D-2-Nal-Arg-LeuNH$_2$, L-1-Nal-Arg-LeuNH$_2$, and L-2-Nal-Arg-LeuNH$_2$ have inhibitory activity against MSH (test Example 1), suppress the melanin formation (text Example 2), and suppress pigmentation in brown guinea pig model (test Example 4), there are no working examples indicating the use of compounds of Formula (1) in regulating immunofunction or regulating appetite in a subject.

(3). The state of the prior art and relative skill of those in the art:

The related art (e.g., references shown in pages 2-3 of the specification) indicates the use of MSH inhibitors have a pigmentation inhibitory activity. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide teachings on the identities of various compounds of formula (1) in whitening, regulating immunofunction or regulating appetite in a subject to be considered enabling for variants.

(4). Predictability or unpredictability of the art:

The claims encompass a method of whitening, regulating immunofunction or regulating appetite in a subject by administering an agent comprising the compound of Formula (1); and a whitening agent comprising the compound of Formula (1), however, the identities of active compounds of Formula (1) and their in vivo effects are not adequately described in the specification, the invention is unpredictable regarding the structures of the compounds of Formula (1) that are effective in the treatment.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method of whitening, regulating immunofunction or regulating appetite in a subject by administering an agent comprising the compound of Formula (1). While the specification discloses specific compounds of Formula (1) such as D-1-Nal-Arg-$LeuNH_2$, D-2-Nal-Arg-$LeuNH_2$, L-1-Nal-Arg-$LeuNH_2$, and L-2-Nal-Arg-$LeuNH_2$ have inhibitory activity against MSH (test Example 1), suppress the melanin formation (text Example 2), and suppress pigmentation in brown guinea pig model (test Example 4), the specification does not describe the use of various compounds of Formula (1) having different substituents in whitening, regulating immunofunction or regulating appetite in a subject. Furthermore, there are no working examples indicating the use of compounds of Formula (1) in regulating immunofunction or regulating appetite in a subject. Since the specification does not provide sufficient teachings on the use of various compounds of Formula (1) that are effective in whitening, regulating immunofunction or regulating appetite in a subject, it is necessary to have additional guidance and to carry out undue experimentation to identify the compounds of Formula (1) that are active in the treatment.

(6). Nature of the Invention

The scope of the claims encompasses a method of whitening, regulating immunofunction or regulating appetite in a subject by administering an agent comprising the compound of Formula (1), but the specification does not provide sufficient teachings on the identities of active compound of Formula (1) and their effects in the treatment. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broader than the enabling disclosure. The working examples do not demonstrate the claimed methods associated with the variants, the effects of

various the compound of Formula (1) are unpredictable, and the teachings in the specification are limited, therefore, it is necessary to carry out undue experimentation to identify the active compound of Formula (1) in the treatment.

New Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1, 4-19 and 24-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. . Claims 1, 4-19 and 24-41 are indefinite because the claim recites "substituents" in R^1, R^2 and $R^3$and/or R^4 in the compound of Formula (I) without defining it, thus it is not clear what group the substituents refer to. Claims 1 and 24 also recites the phrase "or an unsubstituted aminoalkylene group having 1 to 6 carbon atoms and one or more substituents" in X^1, it is not clear how an unsubstituted aminoalkylene group can have one or more substituents. Claims 1 and 24 are also indefinite because of the use of the term "derivable from", it is not clear what is the structure of the amino acid side chain "derivable from" a neutral amino acid, and how different the derived the amino acid side chain is from the parent neutral amino acid side chain. Claims 4-19 and 25-41 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

11. Claims 8-10, 12-14, 16-18, 30-32, 34-36 and 39-40 are indefinite because the claims lack essential steps in the claimed method. The omitted steps are effective amount of the compound

administered and the outcome of the treatment. Claims 8, 12, 16, 30 and 34 are also indefinite as to what has been whitened in an object using the claimed compound.

New Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

12. Claims 24 and 25 are rejected under 35 U.S.C. 102(a) as anticipated by Stewart *et al.* (WO 00/11022, published on March 2, 2000).

Stewart *et al.* teach an anticancer compound such as Ste-2-Nal-Arg (M160), where Ste is stearoyl, CH_3-$(CH_2)_{16}$-C(=O)- (pages 21 and 35). The compound of Ste-2-Nal-Arg corresponds to the compound of formula (1), where n is 1, Ar is 2-naphthyl, X^1 is CH_2, R^1, R^2 and R^3 each is H, R^6 is NHY and Y is CH_3-$(CH_2)_{16}$-C(=O)-, R^4 is arginine side chain, X^2 is single bond, X^3 is O, m is 0, and R^9 is H (claims 24 and 25).

Claim Objections

13. Claims 3 and 20-23 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

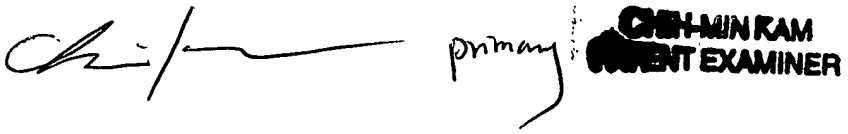
14. Claims 1, 4-19 and 24-41 are rejected, and claims 3 and 20-23 are objected to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.
Primary Patent Examiner



CMK
August 3, 2006